

IMMUNOLOGY AND VACCINE-PREVENTABLE DISEASE

Immunology is a complicated subject, and a detailed discussion of it is beyond the scope of this text. However, an understanding of the basic function of the immune system is useful in order to understand both how vaccines work and the basis of recommendations for their use. The description that follows is simplified. Many excellent immunology textbooks are available to provide additional detail.

Immunity is the ability of the human body to tolerate the presence of material indigenous to the body (“self”), and to eliminate foreign (“non-self”) material. This discriminatory ability provides protection from infectious disease, since most microbes are identified as foreign by the immune system. Immunity to a microbe is usually indicated by the presence of antibody to that organism. Immunity is generally very specific to a single organism or group of closely related organisms. There are two basic mechanisms for acquiring immunity - active and passive.

Active immunity is protection that is produced by the person’s own immune system. This type of immunity is usually permanent.

Passive immunity is protection by products produced by an animal or human, and transferred to another human, usually by injection. Passive immunity often provides effective protection, but this protection wanes (disappears) with time, usually a few weeks or months.

The **immune system** is a complex system of interacting cells whose primary purpose is to identify foreign (“non-self”) substances referred to as **antigens**. Antigens can be either live (such as viruses and bacteria) or inactivated. The immune system develops a defense against the antigen. This defense is known as the **immune response** and usually involves the production of protein molecules, called **antibodies** (or immunoglobulins), and of specific cells (also known as **cell-mediated immunity**) whose purpose is to facilitate the elimination of foreign substances.

The most effective immune responses are generally produced in response to a live antigen. However, an antigen does not necessarily have to be alive, as in a natural infection with a virus or bacteria, to produce an immune response. Some proteins, such as hepatitis B surface antigen, are easily recognized by the immune system. Other material, such as polysaccharide (long chains of sugar molecules that make up the cell wall of certain bacteria) are less effective antigens, and the immune response may not provide as good protection.

PASSIVE IMMUNITY

Passive immunity is the transfer of antibody produced by one human or other animal to another. Passive immunity provides pro-

Principles of Vaccination

Immunity

- Self vs. non-self
- Protection from infectious disease
- Usually indicated by the presence of antibody
- Very specific to a single antigen

Principles of Vaccination

Active Immunity

- Protection produced by the person's own immune system
- Usually permanent

Passive Immunity

- Protection transferred from another person or animal as antibody

Principles of Vaccination

Antigen

- A live or inactivated substance (e.g., protein, polysaccharide) capable of producing an immune response

Antibody

- Protein molecules (immunoglobulin) produced by B lymphocytes to help eliminate an antigen

Passive Immunity

- Transfer of antibody from an exogenous source
- Transplacental most important source in infancy
- Temporary protection

Sources of Passive Immunity

- Almost all blood or blood products
- Homologous pooled human antibody (immune globulin)
- Homologous human hyperimmune globulin
- Heterologous hyperimmune serum (antitoxin)

Monoclonal Antibody

- Derived from a single type, or clone, of antibody-producing cells (B cells)
- Antibody is specific to a single antigen or closely related group of antigens
- Used for diagnosis and therapy of certain cancers, autoimmune conditions, and infectious diseases

tection against some infections, but this protection is temporary. The antibodies will degrade during a period of weeks to months and the recipient will no longer be protected.

The most common form of passive immunity is that which an infant receives from its mother. Antibodies are transported across the placenta during the last 1-2 months of pregnancy. As a result, a full-term infant will have the same antibody "profile" as its mother. These antibodies will protect the infant from certain diseases for up to a year. Protection is better against some diseases (*e.g.*, measles, rubella, tetanus) than others (*e.g.*, polio, pertussis).

Virtually all types of **blood products** contain antibody. Some products (*e.g.*, washed or reconstituted red blood cells) contain a relatively small amount of antibody, and some (*e.g.*, intravenous immune globulin and plasma products) contain very large amounts.

Besides blood products used for transfusion (*e.g.*, whole blood, red cells, and platelets) there are three major sources of antibody used in human medicine. These are homologous pooled human antibody (immune globulin), homologous human hyperimmune globulin, and heterologous hyperimmune serum (antitoxin).

Homologous pooled human antibody is also known as **immune globulin**. It is produced by combining (pooling) the IgG antibody fraction from thousands of adult donors in the U.S. Because it comes from many different donors, it contains antibody to many different antigens. It is used primarily for postexposure prophylaxis for hepatitis A and measles.

Homologous human hyperimmune globulins are antibody products that contain high titers of specific antibody. These products are made from the donated plasma of humans with high levels of the antibody of interest. However, since hyperimmune globulins are from humans, they also contain other antibodies in lesser quantities. Hyperimmune globulins are used for postexposure prophylaxis for several diseases, including hepatitis B, rabies, tetanus, and varicella.

Heterologous hyperimmune serum is also known as **antitoxin**. This product is produced in animals, usually horses (equine), and contains antibodies against only one antigen. In the U.S., antitoxin is available for treatment of botulism and diphtheria. A problem with this product is serum sickness, a reaction to the horse protein.

Immune globulin from human sources is polyclonal - it contains many different kinds of antibodies. In the 1970s, techniques were developed to isolate and "immortalize" (cause to grow indefinitely) single B cells, which led to the development of monoclonal antibody products. Monoclonal antibody is produced from a single clone of B cell, so these products contain antibody to only one antigen or closely related group of antigens. Monoclonal antibody products have many applications, including the diagnosis of certain

types of cancer (colorectal, prostate, ovarian, breast), treatment of cancer (B-cell chronic lymphocytic leukemia, non-Hodgkins lymphoma), prevention of transplant rejection, and treatment of autoimmune diseases (Crohn's disease, rheumatoid arthritis) and infectious disease.

Two globulin products are available for the prevention or treatment of respiratory syncytial virus (RSV) infection - RSV-IGIV and palivizumab (Synagis). RSV-IGIV is a hyperimmune globulin from human donors. It contains antibody other than RSV, like other hyperimmune globulin products. Palivizumab is a humanized monoclonal antibody specific for RSV. It does not contain any other antibody except anti-RSV antibody.

ACTIVE IMMUNITY

Active immunity is stimulation of the immune system to produce antigen-specific humoral (antibody) and cellular immunity. Unlike passive immunity which is temporary, active immunity usually lasts for many years, often for a lifetime.

One way to acquire active immunity is to have the natural disease. In general, once persons recover from infectious diseases, they will be immune to those diseases for the rest of their lives. The persistence of protection for many years after the infection is known as **immunologic memory**. Following exposure of the immune system to an antigen, certain cells (memory B-cells) continue to circulate in the blood (and also reside in the bone marrow) for many years. Upon reexposure to the antigen, these memory cells begin to replicate and produce antibody very rapidly to reestablish protection.

Another way to produce active immunity is by **vaccination**. Vaccines interact with the immune system and often produce an immune response similar to that produced by the natural infection, but do not subject the recipient to the disease and its potential complications. Vaccines produce immunologic memory similar to that acquired by having the natural disease.

Many factors may influence the immune response to vaccination. These include the presence of maternal antibody, nature and dose of antigen, route of administration, and the presence of adjuvants (*e.g.*, aluminum-containing materials added to improve the immunogenicity of the vaccine). Host factors such as age, nutritional factors, genetics, and coexisting disease, may also affect the response.

CLASSIFICATION OF VACCINES

There are two basic types of vaccines: **live attenuated** and **inactivated**. The characteristics of live and inactivated vaccines are different, and these characteristics determine how the vaccine is used.

Live attenuated vaccines are produced by modifying a disease-

Antibody for Prevention of RSV

- RSV-IGIV
 - Human hyperimmune globulin
 - Contains other antibodies
- Palivizumab (Synagis)
 - Monoclonal
 - Contains only RSV antibody

Vaccination

- Active immunity produced by vaccine
- Immunity and immunologic memory similar to natural infection but without risk of disease

Classification of Vaccines

- Live attenuated
 - viral
 - bacterial
- Inactivated

Inactivated Vaccines

- Whole
 - virus
 - bacteria
- Fractional
 - protein-based
 - subunit
 - toxoid
 - polysaccharide-based
 - pure
 - conjugate

producing (“wild”) virus or bacteria in a laboratory. The resulting vaccine organism retains the ability to replicate (grow) and produce immunity, but usually does not cause illness. Live attenuated vaccines available in the U.S. include live viruses and live bacteria.

Inactivated vaccines can be composed of either **whole** viruses or bacteria, or fractions of either. **Fractional** vaccines are either protein-based or polysaccharide-based. Protein-based vaccines include **toxoids** (inactivated bacterial toxin), and **subunit** or sub-virion products. Most polysaccharide-based vaccines are composed of pure cell-wall polysaccharide from bacteria. **Conjugate** polysaccharide vaccines are those in which the polysaccharide is chemically linked to a protein. This linkage makes the polysaccharide a more potent vaccine.

General Rule

The more similar a vaccine is to the natural disease, the better the immune response to the vaccine.

LIVE ATTENUATED VACCINES

Live vaccines are derived from “wild,” or disease-causing, virus or bacteria. These wild viruses or bacteria are attenuated, or weakened, in a laboratory, usually by repeated culturing. For example, the measles vaccine used today was isolated from a child with measles disease in 1954. Almost 10 years of serial passage on tissue culture media was required to transform the wild virus into vaccine virus.

In order to produce an immune response, live attenuated vaccines must replicate (grow) in the vaccinated person. A relatively small dose of virus or bacteria is given, which replicates in the body and creates enough virus to stimulate an immune response. Anything that either damages the live organism in the vial (*e.g.*, heat, light), or interferes with replication of the organism in the body (circulating antibody) can cause the vaccine to be ineffective.

Although live attenuated vaccines replicate, they usually do not cause disease, such as may occur with the natural (“wild”) organism. When a live attenuated vaccine does cause “disease,” it is usually much milder than the natural disease, and is referred to as an adverse reaction.

The immune response to a live attenuated vaccine is virtually identical to that produced by a natural infection. The immune system does not differentiate between an infection with a weakened vaccine virus and an infection with a wild virus. Live attenuated vaccines are generally effective with one dose, except those administered orally.

Live Attenuated Vaccines

- Attenuated (weakened) form of the “wild” virus or bacteria
- Must replicate to be effective
- Immune response similar to natural infection
- Usually effective with one dose

Live attenuated vaccines may cause severe or fatal reactions as a result of uncontrolled replication (growth) of the vaccine virus. This only occurs in persons with immunodeficiency (*e.g.*, from leukemia, treatment with certain drugs, or HIV infection).

A live attenuated vaccine virus could theoretically revert back to its original pathogenic (disease-causing) form. This is known to happen only with live (oral) polio vaccine.

Active immunity from a live attenuated vaccine may not develop due to interference from circulating antibody to the vaccine virus.

Antibody from any source (*e.g.*, transplacental, transfusion) can interfere with growth of the vaccine organism and lead to a poor response or no response to the vaccine (also known as vaccine failure). Measles vaccine virus seems to be most sensitive to circulating antibody. Polio and rotavirus vaccine viruses are least affected.

Live attenuated vaccines are labile, and can be damaged or destroyed by heat and light. They must be handled and stored carefully.

Currently available live attenuated viral vaccines include measles, mumps, rubella, vaccinia, varicella, yellow fever, and influenza (intranasal). Oral polio vaccine is a live viral vaccine but is no longer available in the United States. Live recombinant rotavirus vaccine is still licensed in the U.S. but is no longer distributed because of its association with intussusception. Live attenuated bacterial vaccines include BCG and oral typhoid vaccine.

INACTIVATED VACCINES

These vaccines are produced by growing the bacteria or virus in culture media, then inactivating it with heat and/or chemicals (usually formalin). In the case of fractional vaccines, the organism is further treated to purify only those components to be included in the vaccine (*e.g.*, the polysaccharide capsule of pneumococcus).

Inactivated vaccines are not alive and cannot replicate. The entire dose of antigen is administered in the injection. These vaccines cannot cause disease from infection, even in an immunodeficient person. Unlike live antigens, inactivated antigens are usually not affected by circulating antibody. Inactivated vaccines may be given when antibody is present in the blood (*e.g.*, in infancy, or following receipt of antibody-containing blood products). Inactivated vaccines always require multiple doses. In general, the first dose does not produce protective immunity, but only “primes” the immune system. A protective immune response develops after the second or third dose. In contrast to live vaccines, in which the immune response closely resembles natural infection, the immune response to an inactivated vaccine is mostly humoral. Little or no cellular immunity results. Antibody titers against inactivated antigens fall diminish with time. As a result, some inactivated vaccines may require periodic supplemental doses to increase, or “boost,”

Live Attenuated Vaccines

- Severe reactions possible
- Interference from circulating antibody
- Unstable

Live Attenuated Vaccines

- **Viral** measles, mumps, rubella, vaccinia, varicella, yellow fever, influenza, (oral polio) (rotavirus)
- **Bacterial** BCG, oral typhoid

Vaccines in (parenthesis) are not available in the United States.

Inactivated Vaccines

- Cannot replicate
- Minimal interference from circulating antibody
- Generally not as effective as live vaccines
- Generally require 3-5 doses
- Immune response mostly humoral
- Antibody titer diminishes with time

Principles of Vaccination

Inactivated Vaccines

Whole cell vaccines

- **Viral** polio, hepatitis A, rabies (influenza)
- **Bacterial** (pertussis) (typhoid) (cholera) (plague)

Vaccines in (parenthesis) are not available in the United States.

Inactivated Vaccines

Fractional vaccines

- **Subunit** hepatitis B, influenza, acellular pertussis, (Lyme)
- **Toxoid** diphtheria, tetanus

Vaccines in (parenthesis) are not available in the United States.

Polysaccharide Vaccines

Pure polysaccharide

- pneumococcal
- meningococcal
- *Salmonella typhi* (Vi)

Conjugate polysaccharide

- *Haemophilus influenzae* type b
- pneumococcal

Pure Polysaccharide Vaccines

- Not consistently immunogenic in children <2 years of age
- No booster response
- Antibody with less functional activity
- Immunogenicity improved by conjugation

antibody titers.

Currently available inactivated vaccines are limited to inactivated whole viral vaccines (influenza, polio, rabies, and hepatitis A).

Whole inactivated bacterial vaccines (pertussis, typhoid, cholera, and plague) are no longer available in the United States.

“Fractional” vaccines include subunits (hepatitis B, influenza, acellular pertussis), and toxoids (diphtheria, tetanus). A subunit vaccine for Lyme disease is no longer available in the U.S.

POLYSACCHARIDE VACCINES

Polysaccharide vaccines are a unique type of inactivated subunit vaccine composed of long chains of sugar molecules that make up the surface capsule of certain bacteria. Pure polysaccharide vaccines are available for three diseases: pneumococcal disease, meningococcal disease, and *Salmonella typhi*. A pure polysaccharide vaccine for *Haemophilus influenzae* type b is no longer available in the U.S.

The immune response to a pure polysaccharide vaccine is typically T-cell independent, which means that these vaccines are able to stimulate B-cells without the assistance of T-helper cells. T-cell independent antigens, including polysaccharide vaccines, are not consistently immunogenic in children <2 years of age. Young children do not respond consistently to polysaccharide antigens, probably because of immaturity of the immune system.

Repeated doses of most inactivated protein vaccines cause the antibody titer to go progressively higher, or “boost.” Repeat doses of polysaccharide vaccines do not cause a booster response. This is not seen with polysaccharide antigens. Antibody induced with polysaccharide vaccines has less functional activity than that induced by protein antigens. This is because the predominant antibody produced in response to most polysaccharide vaccines is IgM, and little IgG is produced.

In the late 1980s, it was discovered that the problems noted above could be overcome through a process called **conjugation**. Conjugation changes the immune response from T-cell independent to T-cell dependent, leading to increased immunogenicity in infants and antibody booster response to multiple doses of vaccine.

The first conjugated polysaccharide vaccine was for *Haemophilus influenzae* type b (Hib). A conjugate vaccine for pneumococcal disease was licensed in 2000. A meningococcal conjugate vaccine may be available in the future.

RECOMBINANT VACCINES

Vaccine antigens may also be produced by genetic engineering technology. These products are sometimes referred to as **recombinant** vaccines. Three genetically-engineered vaccines are currently available in the United States. Hepatitis B vaccines are pro-

duced by insertion of a segment of the hepatitis B virus gene into the gene of a yeast cell. The modified yeast cell produces pure hepatitis B surface antigen when it grows. Live typhoid vaccine (Ty21a) is *Salmonella typhi* bacteria that has been genetically modified to not cause illness. Live attenuated influenza vaccine (LAIV) has been engineered to replicate effectively in the mucosa of the nasopharynx but not in the lungs.

SELECTED REFERENCES

Ada G. The immunology of vaccination. In: Plotkin SA, Orenstein WA. *Vaccines*. 4th ed. Philadelphia, PA: Saunders, 2003:31-45.